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DUPLICATE

Thomas P Koestler, Ph.D.
Vice President Head

Novartis Pharmaceuticals Corporation
World Wide Drug Regulatory Affairs
59 Route 10
East Hanover NJ 07936-1080

NOVARTIS

COPY FOR YOUR
INFORMATION

NC
NEW CORRESP

March 19, 1997

US Tel 201 503 5757
US Fax 201 503 5544

Basle/Switzerland
Tel 061 324 48 07
Fax 061 324 84 83

REVIEWS COMPLETED

CSO ACTION.

☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS

DATE

Hand-Delivered

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research
Suite 6027-42
1451 Rockville Pike
Rockville, Maryland 20850

SANDIMMUNE® (cyclosporine)

Approved NDA 50-573

Approved NDA 50-574

Approved NDA 50-625

NEORAL® (cyclosporine for microemulsion)

Approved NDA 50-715

Approved NDA 50-716

Pending NDA 50-735

Pending NDA 50-736

~~Pending~~ NDA 50-737

Pending NDA 50-738

Dear Dr. Lumpkin:

Reference is made to your letter dated April 19, 1995, which responds to our request that Novartis' (then Sandoz's) applications for Sandimmune® (cyclosporine) and Neoral® (cyclosporine for microemulsion) be reclassified as drugs submitted and approved pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act ("the Act"). As indicated by Novartis' Request for Reclassification and our subsequent discussions, the issue of cyclosporine's classification as an "antibiotic drug" under section 507 of the Act has always been critically important to us. Now, due to the impending action on four supplemental applications (for autoimmune indications for cyclosporine), the "antibiotic drug" classification has taken on even greater significance.

As you know, the Agency is expected to take action on Novartis' supplemental applications for use of Neoral® in treating rheumatoid arthritis (RA) and psoriasis. Like the original new drug applications (NDAs) for Sandimmune® and Neoral®, these supplemental applications are based upon significant research conducted by Novartis. Moreover, it is expected that the ultimate, potential approval of the RA supplemental application will be contingent upon Novartis' commitment to satisfy additional, Phase IV research obligations. In addition, following final action on its pending supplemental applications, Novartis will have paid

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\$447,000.00 in user fees pursuant to the Prescription Drug User Fee Act (PDUFA) to support review and final action on its Neoral® applications.

Despite the research Novartis has already conducted and will be required to continue to conduct as a condition of approval of its cyclosporine products, the Company has not been granted any statutory incentives in recognition of its research investments. In fact, because of cyclosporine's antibiotic classification, the Company will not even receive three years of so-called "promotional exclusivity" for the critically important RA and psoriasis indications that are expected to be added to the Neoral® labeling.

Because of the obvious inequities posed by this situation, Novartis is following up on your offer to let us address the Agency's decision to continue regulating cyclosporine products under section 507 of the Act. As you know, Novartis' Request for Reclassification responded to the Agency's interest in scientific issues related to the antibiotic classification of cyclosporine. Although we continue to believe that there is no valid scientific basis to classify cyclosporine as an antibiotic, there are even more fundamental issues that must first be addressed in connection with the Request for Reclassification.

Most importantly, there is the issue of a "level playing field." We have identified several products similar to cyclosporine with respect to its "antibiotic" classification but that nonetheless are regulated as, and enjoy the benefits of their status as, "drugs" under section 505 of the Act. (Similarly, we have identified antibacterial agents approved for treatment of infections that also are regulated as section 505 "drugs.")

The most notable similarly-situated product is Mevacor® (lovastatin) -- a novel fungal metabolite discovered when it was produced from a strain of *Aspergillus terreus* obtained in a soil isolation program. Lovastatin is obviously similar to cyclosporine in its fungal derivation and antifungal properties. Yet, the Agency classifies lovastatin as a drug under section 505. There is simply no reason, scientific or otherwise, for lovastatin and cyclosporine to be treated differently under the Act.

The classification of lovastatin (and several antibacterial agents) as section 505 drugs points to the larger issue: the lack of reasonable, articulated standards that have been subjected to scientific input and critical public scrutiny, that are known to all interested persons, and that are applied consistently to each application filed by the Agency. Undoubtedly, it has been the lack of such standards that has caused the Agency's inconsistent treatment over the years of the Sandimmune® and Neoral® applications. Almost without exception, the Agency has initially assigned section 505 drug NDA numbers to the Sandimmune® and Neoral®

applications. Only after these applications were submitted did the Agency apparently reconsider its original designations and reclassify the applications as antibiotics. Over the years, the rationale for these various reclassifications of cyclosporine also has changed. For example, the original reclassification decision in 1982 apparently was triggered by an interest in applying the section 507 batch certification requirements to the original Sandimmune® application. Only in 1994-1995 were scientific issues raised with respect to the classification of cyclosporine as an antibiotic. In the interim, FDA continued to assign section 505 drug NDA numbers to most cyclosporine applications.

Finally, there is the issue of Congress' intent in codifying the definition of "antibiotic drug." Although this issue was first raised in the Agency's response to our Reclassification Request, Novartis has now conducted a comprehensive review of the legislative history of the 1962 Amendments to the Act. We have found nothing in the legislative history to indicate that Congress intended to single out products that are produced by fermentation. Rather, we have found a clear Congressional intent to cover only true "antibiotics" indicated for antibiotic uses. For example, a report by a special advisory committee of the National Academy of Sciences-National Research Counsel submitted to and adopted by the Secretary of Health, Education, and Welfare (HEW) recommended: "The FDA should be given statutory authority to apply certification procedures to all antimicrobial agents used in the prophylaxis and treatment of infectious diseases." See *Drug Industry Antitrust Act, Hearings On S. 1552 Before the Subcomm. On Antitrust and Monopoly of the Senate Comm. on the Judiciary*, 87th Cong., 1st Sess., Part 2, Exhibits And Appendix, 460, reprinted in FDA, A LEGISLATIVE HISTORY OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND ITS AMENDMENTS, Vol. XVIII, at 220. Similarly, in urging Congress to adopt the provision, the Secretary of HEW repeatedly referred to the use of "antibiotic drugs" to be covered under section 507 "in the treatment of infectious diseases." *Drug Industry Antitrust Act Hearings*, Part 5, at 2589-90 (testimony of Secretary Ribicoff), reprinted in, FDA, A LEGISLATIVE HISTORY, Vol. XX, at 331-32. Thus, there is even a more compelling need to develop consistently-applied standards, based upon public input, that will effectuate Congress' intent.

If such standards had been promulgated and codified in the Agency's antibiotic regulations, Novartis is confident that Sandimmune® and Neoral® would be regulated as drugs under section 505(b) of the Act. To redress the current situation -- particularly given the lack of a "level playing field" and Congress' clear intent to classify as antibiotics those products that (unlike cyclosporine) treat infectious diseases -- Novartis believes the Agency must immediately reclassify cyclosporine as a drug under section 505(b). At the very least, pending development of codified standards and their application to Sandimmune® and Neoral®, the Agency must not

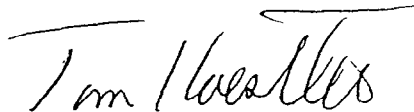
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take any action that further deprives Novartis of rights to which it otherwise would be entitled if these products were properly classified as drugs under section 505(b).

Given the pressing nature of the classification issue in the context of the impending action on the RA and psoriasis applications, Novartis would like to accept your invitation to meet with appropriate officials in the Center to discuss this matter in greater detail. We request that such a meeting be convened by the first week of April so a final decision can be rendered prior to action on our pending supplemental applications.

We look forward to working with the Center to resolve this urgent matter.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Tom Koestler". The signature is fluid and cursive, with a horizontal line above the first part of the name.

Thomas P. Koestler, Ph.D.
Vice President, Head
World Wide Drug Regulatory Affairs

cc: Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20857



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

April 19, 1995

Food and Drug Administration
Rockville MD 20857

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Thomas P. Koestler, Ph.D.
Vice President, Corporate Head
Drug Registration and Regulatory Affairs
Sandoz Pharmaceuticals Corporation
59 Route Ten
East Hanover, New Jersey 07936-1080

Dear Dr. Koestler,

On October 14, 1994 and February 28, 1995 you wrote letters to the Center for Drug Evaluation and Research (CDER) requesting that your applications for SANDIMMUNE (cyclosporine) and NEORAL (cyclosporine, microemulsion) be reclassified as drugs under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act). Presently they are classified as antibiotics under section 507 of the Act.

After reviewing the information submitted by Sandoz to support this request, I am now able to inform you that CDER intends to continue to regulate these products under section 507 of the Act.

As we both agree, the manufacture of cyclosporine involves a fermentative process employing a microorganism, and, as such, it meets the first part of the statutory definition of an antibiotic. Thus, the crux of the classification decision rests on whether cyclosporine has the capacity to inhibit or destroy microorganisms in dilute solution . . . (21 U.S.C. 357).

We do find, based on the information we presently have, that cyclosporine can indeed inhibit or kill certain human pathogens *in vitro* at concentrations that are relevant to those found in the human body when cyclosporine is used clinically as described in its approved or proposed labeling. For your convenience, I have appended to this letter, a copy of the microbiologist's report from HFD-530 summarizing our analysis of cyclosporine's antimicrobial capacity. Cyclosporine meets both parts of the statutory definition of products that must be regulated under section 507.

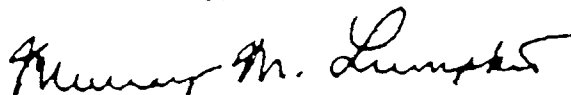
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In our review of the legislative history of section 507 of the Act, we found no Congressional reference as to how the term "inhibits or destroys microorganisms in dilute solution" should be interpreted. However, we believe our findings are consistent with the ordinary meaning of the words in the statute and with Congressional intent to single out those drugs, such as cyclosporine, which are produced by a fermentative process. In addition, the FDA has a strong history of interpreting section 507 without reference to whether the product is used clinically as an antibiotic. Several anti-neoplastic agents have been classified as Section 507 products because they meet the legal definition of an "antibiotic drug".

I realize that the classification of cyclosporine is of significant importance to Sandoz. Thus, if you or your staff believe we have misinterpreted the scientific information you submitted or that we have misinterpreted the intent of the law, please do not hesitate to let me know. I would be happy to facilitate a meeting with the scientific and legal staff of the Center to discuss this further if you feel such would be helpful.

Yours sincerely,



Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

cc: Janet Woodcock, M.D.
Amanda Pedersen, J.D.
Ann Wion, J.D.
David Fox, J.D.
David Felgal, M.D.
James Bilstad, M.D.
Jane Axelrad, J.D.